

## ORIGINAL PAPER

**EXACT: rivastigmine improves the high prevalence of attention deficits and mood and behaviour symptoms in Alzheimer's disease\***S. Gauthier,<sup>1</sup> A. Juby,<sup>2</sup> B. Rehel,<sup>3</sup> R. Schecter<sup>3</sup>**OnlineOpen:** This article is available free online at [www.blackwell-synergy.com](http://www.blackwell-synergy.com)

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**SUMMARY**

The objective of this study was to investigate the impact of rivastigmine therapy on attention, apathy, anxiety and agitation in patients with mild-to-moderate Alzheimer's disease (AD) in a real-world clinical setting. Patients with mild-to-moderate AD were enrolled in the study by physicians across Canada. They were treated with open-label rivastigmine (dose at the discretion of the prescribing physicians) for a period of 6 months. Changes from baseline in attention, apathy, anxiety and agitation were assessed using an abbreviated Clinician's Global Impression of Change at 3- and 6-month visits. The Mini Mental State Examination (MMSE) was also used at these visits. Use and changes in use of psychotropic medications were recorded, as were changes in caregiver burden. Analyses of subgroups (outpatients vs. institutionalised patients) were also performed. A total of 2119 patients were enrolled in the study by 375 physicians. At baseline, 91% had deficits in attention, 85.4% had symptoms of anxiety, 78.5% exhibited apathy and 70.1% showed agitation. At 6 months, 67.5% of evaluable patients had improved on the symptom of attention, while 62.3%, 62.6% and 56.0% had improvements in anxiety, apathy and agitation respectively. The percentages with improvements were higher in the institutional subgroup than among outpatients. There was an overall mean improvement of 1.1 points on the MMSE at 6 months. Approximately four times as many caregivers reported a reduced burden than an increased burden at 6 months (40.3% vs. 10.3%). The majority of patients treated with rivastigmine experienced improvements in attention, anxiety, apathy and agitation. These real-life findings further demonstrate the proven efficacy of rivastigmine in patients with mild-to-moderate AD.

**Introduction**

The use of cholinesterase inhibitors (ChEIs) for the treatment of Alzheimer's disease (AD) began in Canada in 1997, representing a significant advance in treatment at that time. Three ChEIs are currently approved in Canada for the symptomatic treatment of AD: donepezil (Aricept®; Pfizer, New York, NY), rivastigmine (Exelon\*, Novartis, Basel, Switzerland) and galantamine (Reminyl®; Janssen Ortho, Titusville, NJ). While all increase the level of acetylcholine (ACh) in the brain, they differ substantially in mechanism of action, inhibitory potency, brain selectivity and metabolism.

Rivastigmine is the only approved ChEI that targets both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Importantly, the pathophysiological changes associated with AD are

**What's known**

- In placebo-controlled clinical trials in Alzheimer's disease, rivastigmine has been shown to be effective in improving cognition, neuropsychiatric symptoms, activities of daily living and global function.
- Attention, anxiety, apathy and agitation are known to be common symptoms in Alzheimer's disease.
- In placebo-controlled clinical trials, caregiver burden has been reduced by administering cholinesterase inhibitors.

**What's new**

- This article assesses the prevalence of attention deficits, anxiety, apathy and agitation in a non-selected, real-world cohort of AD patients treated in the community.
- It evaluates rivastigmine therapy in this real-world, non-standardised clinical setting.
- It shows how clinicians can use simple tools (i.e. the modified Clinical Global Impression of Change scale) to assess and monitor their patients in routine practice.

associated with an increased ratio of BuChE-to-AChE expression in the limbic system and cortex (2–4).

Alzheimer's disease is characterised by a progressive cholinergic denervation in specific regions of the forebrain, particularly the hippocampus and neocortex (5). As cognitive dysfunction ensues, the loss of ACh-producing neurons in major brain areas also leads to an impaired ability to perform activities of daily living (ADL), problems with attention (lack of concentration/distractibility) and the emergence of mood and behavioural symptoms (6).

Most of the earlier trials of pharmacotherapies for AD focused primarily on the domain of cognition (i.e. memory loss). However, one of the most important early benefits of ChEIs is on the subcognitive domain of attention. Patients with AD are often described by caregivers as being unable to concen-

trate, easily distractible or getting confused by tasks that were previously easily performed. It is thought that deficits in attention may underlie the difficulties with everyday activities in the early stages of AD (7).

In addition, mood and behavioural symptoms (e.g. apathy, anxiety and agitation) are very common in AD, affecting up to 80% of a typical clinical population (8,9). Mood and behavioural symptoms are prevalent in the early stages of AD and their occurrence may precede a diagnosis by up to 3 years (9). Once present, these symptoms tend to worsen, becoming more prominent and recurrent manifestations of the disease (10).

The most frequently reported mood and behavioural symptoms are apathy (exhibited by 70% of patients), agitation (occurring in 60% of patients) and anxiety (48% of patients); irritability, dysphoria, aberrant motor behaviour, disinhibition, delusions and hallucinations are also common manifestations (9).

In the presence of these symptoms, normal functioning deteriorates and quality of life is reduced, both for the patient and the caregiver (11). As severity increases, these symptoms can add to caregiver distress and often lead to institutionalisation of the patient (12).

Thus, the effective treatment of mood and behavioural symptoms in AD has the important potential to reduce the personal, social and economic burden of dementia. Indeed, the importance of treating AD-related mood and behavioural symptoms is underscored by recommendations that measures of improvement in mood and behaviour be included in all new clinical trials for AD (13,14). Some AD specialists have begun to consider ChEIs in the management of AD-related attention and mood and behavioural disturbances.

### Study rationale

Emerging clinical data suggest that, in addition to their cognitive benefits, ChEIs may improve or delay such symptoms as attention deficits or mood and behavioural disturbances of AD. Medications with regional specificity for brain areas most affected in AD might have the potential to provide a more effective treatment for AD-related mood and behavioural symptoms (15). Rivastigmine has demonstrated broad benefits across cognitive and functional domains of AD (16–19). Data also indicate that treatment with rivastigmine as early as possible in the disease process is likely to offer the best chance of maintaining long-term function (20). Most importantly, preliminary information from several open-label studies, including EXTEND (21), have demonstrated that the effect of rivastigmine on

mood and behaviour might be more significant than previously surmised and, perhaps, even more clinically meaningful than the benefit on cognition. Rivastigmine may improve and/or delay the symptoms of mood and behaviour (17,22,23), particularly with respect to the symptoms of apathy, anxiety and agitation, while reducing and/or delaying the use of concomitant psychotropic medications (24,25).

### Study objectives

The primary objective of the EXACT (Exelon\* Therapy to ACT on the four As of AD) study was to evaluate the efficacy of rivastigmine in the management of the symptoms of attention, apathy, anxiety and agitation (the 'four As of AD') in patients with AD in a real-world clinical setting. A secondary objective was to evaluate the use of concomitant psychotropic medications during treatment with rivastigmine.

### Study population

For inclusion into the study, patients had to meet the following inclusion criteria: clinical diagnosis of mild-to-moderate AD (MMSE  $\geq 10$  and  $\leq 26$ ) and for which rivastigmine treatment is deemed appropriate according to the treating physician; living in the community or institutionalised; having a regular informant/caregiver (at least three contacts per week) and able to give written, informed consent (or having a legal representative who can give written, informed consent).

Patients who met any of the following criteria were excluded from participation: patients with a known hypersensitivity to rivastigmine or its components; patients with a medical condition that represents a contraindication to rivastigmine; female patients of child-bearing potential; patients who have been initiated on a psychotropic medication within the last 2 months and patients taking an investigational drug or participating in another study.

### Methodology

EXACT was a naturalistic, multi-centre, observational study, the methodology of which was designed by an independent Steering Committee of AD specialists. Before the start of the study, the protocol, patient informed consent and any other appropriate documents were submitted to an independent ethics committee and all ethical requirements were met.

Physicians enrolled in the study received an introductory letter by mail to explain the objectives and format of the study. They were then subject to a Study Site Initiation, intended to update participating physicians on applicable good clinical practice

requirements, to present and review details of the conduct of the study to the investigator and all appropriate site personnel, and to provide an opportunity for the staff to collectively resolve any questions or problems related to the study.

As this was an observational study, the decision to initiate ChEI therapy with rivastigmine was made as per normal medical practice prior to the patient's participation in the study. This study sought only to collect information on patients meeting the appropriate entry criteria.

### Intervention

All patients in the EXACT study were enrolled on the basis of having been prescribed rivastigmine recently. To ensure that patients were using rivastigmine appropriately, physicians were asked to instruct their patients on appropriate dosing. The following recommendations were provided as a guide only, as individual tolerance to increases in dose may vary:

- a. Start at rivastigmine 1.5 mg b.i.d. (with breakfast and dinner) for 4 weeks.
- b. Increase to therapeutic dose of 3 mg b.i.d. (with breakfast and dinner).

For many patients, no further dose increase may be required. However, dose increases above 3 mg b.i.d. could be considered following a complete evaluation of the patient's condition. Some patients may derive additional benefits by further increasing the dose of rivastigmine to 4.5 mg b.i.d. after a minimum of 4 weeks on the previous dose. If even greater efficacy is required, a final dose increase to 6 mg b.i.d. was possible. It was recommended according to the study protocol that this increase should be carried out only after a minimum of 4 weeks on the previous dose.

Each patient was enrolled in the EXACT study for a period of 6 months. The patient (or his/her medication insurance plan, if applicable) was responsible for the cost of rivastigmine.

### Variables assessed

The primary efficacy variables used in this study were the abbreviated Clinical Global Impression of Change scale (CGI-C) and the Mini Mental State Examination (MMSE, performed according to provincial requirements). The abbreviated CGI-C scale was used to assess the symptoms of attention, apathy, anxiety and agitation. The following subdomains of the CGI-C were used to assess the severity of the patient's symptoms within each domain:

- Attention = concentration / distractibility
- Apathy = indifference / diminished initiative / lesser involvement in usual activity
- Anxiety = worrying / ruminations / nervousness

- Agitation = restlessness / pacing / unwarranted requests/repetitive sentences

At baseline, clinicians were asked to rate each patient as normal or mildly, moderately or severely impaired for each of the four symptoms. At 3 and 6 months, physicians rated their impression of change as improved (markedly, moderately or minimally), worsened (markedly, moderately or minimally) or unchanged.

Caregiver burden was assessed; caregivers were asked to rate the burden of caring for the patient as 'not present', 'mild', 'moderate' or 'severe' at baseline and at months 3 and 6.

The pattern of use of psychotropic medications (antipsychotics, anxiolytics, antidepressants, hypnotics and mood stabilisers) was also tracked at baseline, 3 and 6 months.

Safety and tolerability were assessed by recording adverse events and serious adverse events.

Study physicians were required to report any serious adverse event occurring in a patient after providing informed consent and until 4 weeks after the patient ended participation in the study.

While study physicians were asked to record all adverse events, with such a large number of trial investigators ( $n = 375$ , mostly primary-care clinicians) the steering committee decided that for this type of naturalistic study, the inter-investigator variability in adverse event reporting would be vast, reducing the chances of obtaining valid adverse event information.

Furthermore, rivastigmine is an agent with a long-track record of clinical use and a significant body of safety evidence from placebo-controlled clinical trials. The objective of this study was to evaluate the efficacy of the drug in a real-life, naturalistic manner. As such, the steering committee decided not to attempt to assess and report overall safety and tolerability in this cohort.

### Data collection and follow-up

The prescribing physician collected information from the patient at registration and at two additional visits: (1) a 3-month postregistration consultation and (2) a 6-month postregistration consultation.

Apart from the two study-required visits, physicians were asked not to deviate from their regular medical practice, scheduling patient visits as deemed necessary. The patient's medical care was at the entire discretion of the physician.

Patients were free to withdraw from the EXACT study at any time or could be withdrawn by their physician for any reason. Physicians were asked to note the reasons for withdrawal on the Case Report Form.

## Data analysis

The results are presented based on the intention-to-treat approach. Analysis of the efficacy end-points consisted of summary statistics for observed cases. Imputation methods were not used for missing data.

The CGI-C and MMSE were analysed and summarised using descriptive statistical methods. In all cases where they were collected, the average MMSE scores were summarised using mean and standard deviation values between registration and the final study visit. For all patients enrolled in the study, the CGI-C scores obtained at visits 2 and 3 were described with respect to the baseline symptom evaluation using a frequency distribution (frequencies and proportions). For visit 1, the use of psychotropic concomitant medications (drug class, name and dose) was assessed using a frequency distribution. For both subsequent visits, changes in the intent to use these concomitant medications (same dose; higher dose, lower dose; discontinuation; use of new medication) were assessed using frequencies and proportions.

## Results

### Baseline demographics

A total of 2119 patients were enrolled in the study by 375 physicians across Canada. Of these, 1652 (78.1%) were outpatients, 433 (20.4%) were living in institutional settings and 34 (1.6%) were registered as unknown. Baseline demographics are summarised in Table 1. The mean age of the participants was 81.7 years, women made up 60.1% of the cohort and the mean duration of AD since diagnosis was 2.1 years.

For three-quarters of patients in the study (74.4%), rivastigmine was the first ChE inhibitor prescribed. One-fifth of patients (366 patients, 20%) had previously been treated with donepezil, 71 patients (3.9%) with galantamine and 20 patients (1.1%) with both donepezil and galantamine.

### Participant attrition

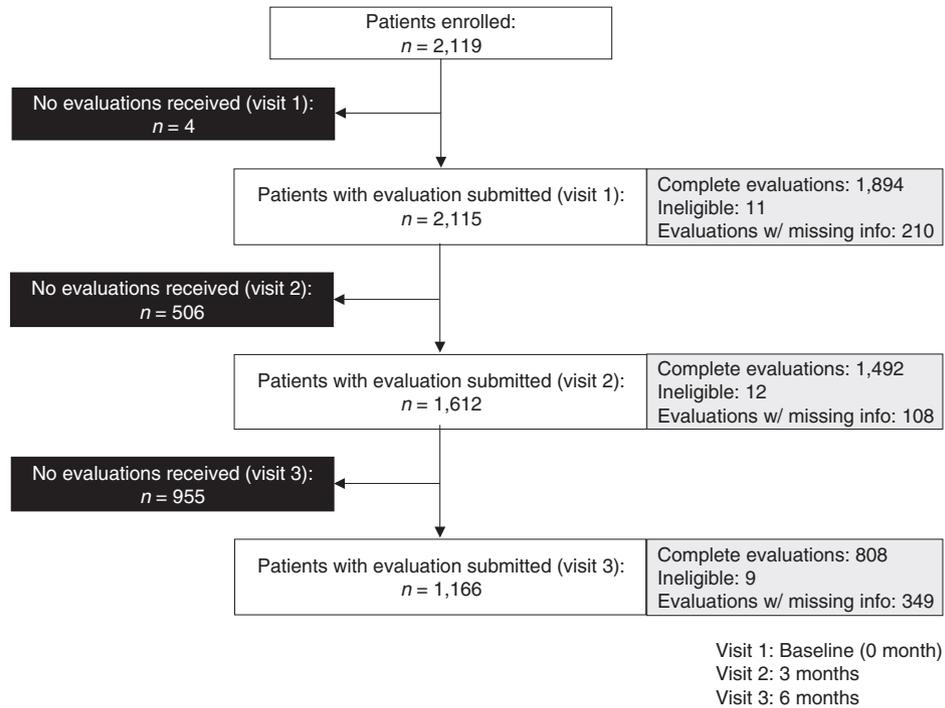
Of the 2119 patients enrolled, 2115 (99.8%) received a baseline evaluation; 1612 (76.1%) had valid case report forms at 3 months and 1166 (55.0%) were evaluable at 6 months (Figure 1). The majority of the missing information was due to the fact that evaluations were not returned by the study physicians for many of their patients. At 3 months, for example, evaluations were not received for 506 patients. At the 6-month visit, evaluations were not received for 955 patients. Whether these patients had dropped out or their physicians simply had not submitted the records is unknown.

In addition to unreturned records, many study physicians returned incomplete evaluations. At the baseline visit, there were 210 incomplete evaluations; at 3 months, 108 of the 1612 evaluations were incomplete and at 6 months, 349 of 1166 were incomplete. Incomplete records were used in the analyses when the relevant data were present. Because of this, the total number of patients evaluated varies from end-point to end-point within these results.

The proportion of evaluable outpatients to inpatients remained relatively constant throughout the study, with a small and gradual shift towards a larger proportion of inpatients. At baseline, the proportion

**Table 1** Baseline demographics by enrolment criteria (all patients enrolled)

Characteristic	Overall	Outpatient	Institutionalised	Unknown
Age (years)				
n	2087	1632	431	24
Mean	81.7	80.8	84.9	83.5
SD	8.15	8.1	7.55	6.77
Range	30–105	36–104	30–105	72–102
Gender				
n	2119	1652	433	34
Men (%)	821 (38.7)	690 (41.8)	123 (28.4)	8 (23.5)
Women (%)	1273 (60.1)	953 (57.7)	306 (70.7)	14 (41.2)
Unknown (%)	25 (1.2)	9 (0.5)	4 (0.9)	12 (35.3)
Duration of AD (years)				
n	1832	1423	388	21
Mean	2.1	2.0	3.2	2.1
SD	2.01	1.81	2.41	1.44
Range	0–25	0–25	0–16	0.5–6



**Figure 1** Participant flow

was 78.1/20.4; at visit 2, it was 77.4/21.8 and at visit 3, it was 76.6/23.1.

The proportion of evaluable drug-naïve patients vs. those switched from other ChEIs (approximately 3 : 1) remained constant throughout the study.

There were 99 patient records available at visit 3 with documented reasons for withdrawal of study medication. Nausea was the most common adverse effect cited as a reason for withdrawal (24 of 99 withdrawals, 24.2%).

### Rivastigmine dose

Of the 1166 patients at 6 months, there were a total of 1063 patients (91.2%) still using rivastigmine, with 99 no longer using the drug and four for whom the answer was not provided. The 3.0 mg b.i.d. regimen was the most common at 6 months (642 patients, 60.4% of patients), while 156 (14.7%) finished the study on the 4.5 mg b.i.d. regimen and 44 (4.1%) completed the study taking rivastigmine 6.0 mg b.i.d.

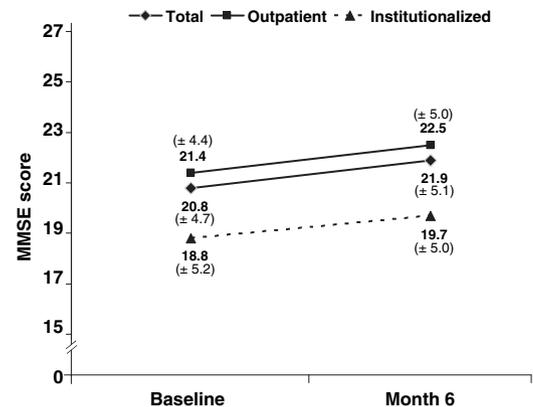
### MMSE results

Of a possible total score of 30, the overall average MMSE score at baseline was 20.8 ( $\pm 4.7$  standard deviation). Not surprisingly, the mean baseline MMSE score was considerably higher for the outpatient group ( $21.4 \pm 4.4$ ) than for the institutionalised group ( $18.8 \pm 5.2$ ).

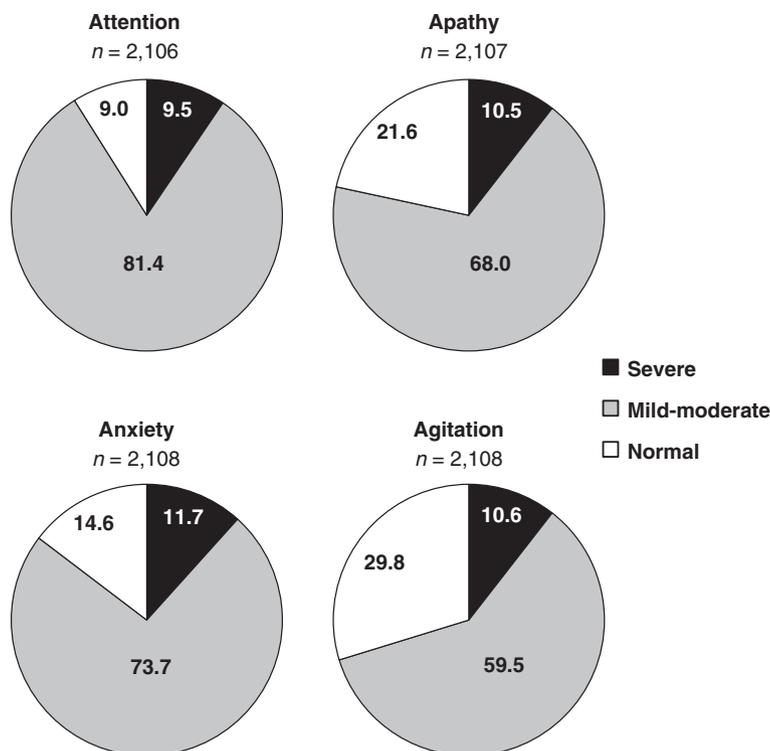
At 6 months, both groups had improved from baseline, with the mean score increasing in the outpatient group to a total mean score of 22.5 ( $\pm 5.0$ ) and in the institutionalised group to 19.7 ( $\pm 5.0$ ). The overall mean MMSE score increased from 20.8 to 21.9 ( $\pm 5.1$ ) (Figure 2).

### Severity at baseline

At the initial visit, there was a high prevalence of the four symptoms under investigation. Attention deficits were present in 91% (1916/2106) of patients. Of the total population, 81.4% had mild-moderate attention



**Figure 2** Mean ( $\pm$ SD) changes in Mini Mental State Examination (MMSE) from baseline (observed cases)



**Figure 3** Baseline prevalence (%) and severity of attention difficulties, anxiety, apathy and agitation (observed cases)

deficits, while 9.5% had severe deficits and 9.0% had no deficit.

More than 85% of patients demonstrated anxiety at baseline (73.7% mild-moderate, 11.7% severe), while almost 80% demonstrated apathy (68% mild-moderate, 10.5% severe) and more than 70% showed signs of agitation (59.5% mild-moderate, 10.6% severe) (Figure 3).

The coexistence of symptoms was very common (Table 2). At baseline, the number of patients with all four of anxiety, apathy, agitation and attention deficits was 1143 (54.0%). A further 517 (24.5%) had three of the four and 312 (14.8%) had two of the four symptoms. There were 103 patients (4.9%)

with only one of the four symptoms and 33 patients (1.6%) with none.

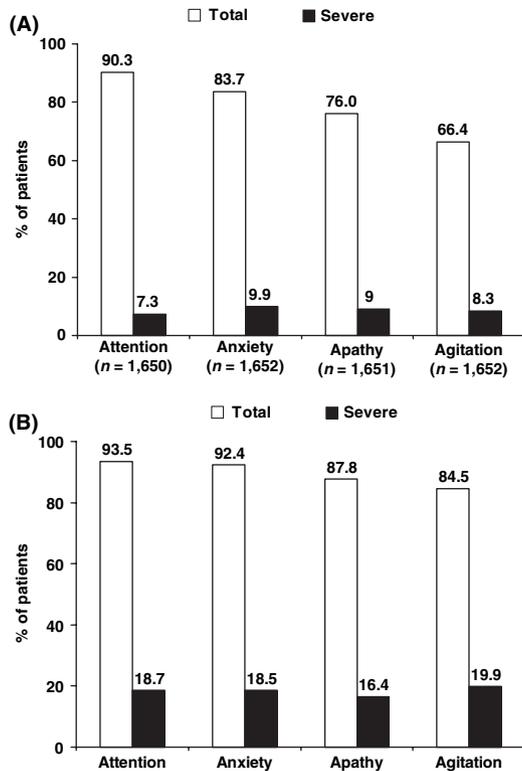
The prevalence of these symptoms was also recorded based on site of care. A total of 93.5% of institutionalised patients had attention difficulties, including 18.7% of the total cohort whose difficulties were assessed as severe. Among institutionalised patients, 92.4% had anxiety, with 18.5% classified as severe; 87.8% of institutionalised patients demonstrated apathy, including 16.4% with severe symptoms. Finally, 84.5% of patients demonstrated agitation, including 19.9% in whom this was judged to be severe. The prevalence of each symptom (broken down by total and severe) is shown in Figure 4(A,B) for outpatients and institutionalised patients respectively.

**Table 2** Number and percentage of patients with anxiety, agitation, apathy and attention difficulties at baseline

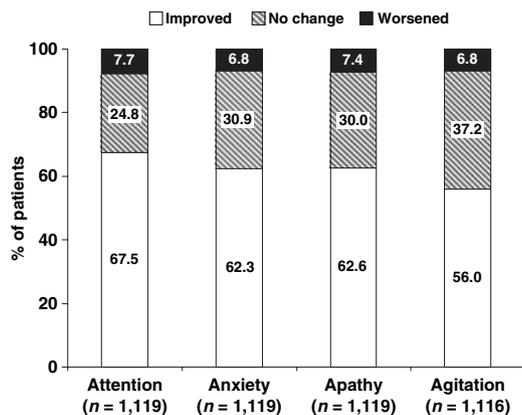
Number of symptoms	n (%)
0 symptoms	33 (1.6)
1 symptom	103 (4.9)
2 symptoms	312 (14.8)
3 symptoms	517 (24.5)
4 symptoms	1143 (54.2)
Total	2108 (100)

### CGI-C results

Overall, in each of the four symptoms, the majority of patients for whom records were submitted improved on rivastigmine therapy at 6 months, while some patients remained unchanged and only a small percentage was deemed to have worsened. In the symptom of attention, 67.5% of evaluable patients improved, while 24.8% remained unchanged and 7.7% worsened. The corresponding figures for anxiety were 62.3%, 30.9% and 6.8%; for apathy 62.6%, 30.0% and 7.4% and for agitation 56.0%, 37.2% and 6.8% respectively (Figure 5).

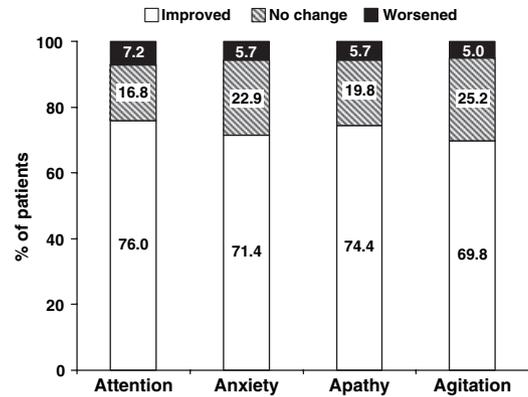


**Figure 4** (A) Prevalence and severity of attention difficulties, anxiety, apathy and agitation among outpatients at 6 months (observed cases). (B) Prevalence and severity of attention difficulties, anxiety, apathy and agitation among institutionalised patients at 6 months (observed cases,  $n = 433$ )

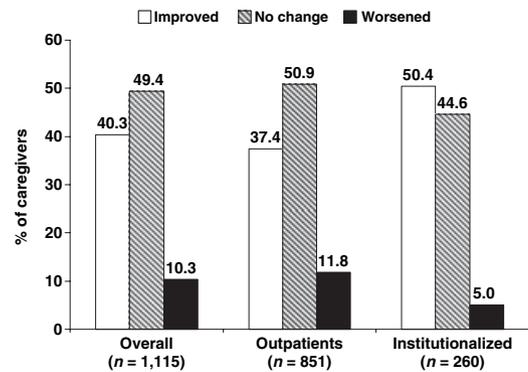


**Figure 5** Proportion of patients experiencing improvement, no change or worsening of attention difficulties, anxiety, apathy and agitation at 6 months (observed cases)

In the institutional setting, for the symptoms of attention, anxiety, apathy and agitation, 76.0%, 71.4%, 74.4% and 69.8% of patients with available records showed improvement, while only 7.2%, 5.7%, 5.7% and 5.0% worsened respectively (Figure 6).



**Figure 6** Proportion of patients experiencing improvement, no change or worsening of attention difficulties, anxiety, apathy and agitation at 6 months (observed cases, institutionalised cohort,  $n = 262$ )



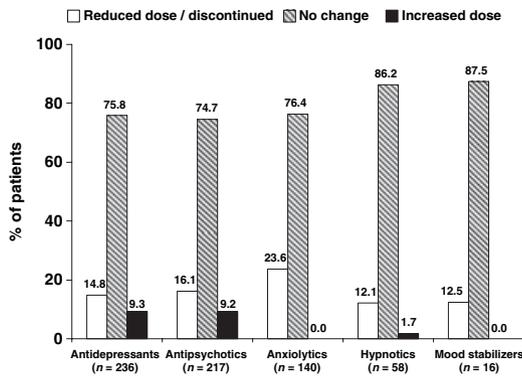
**Figure 7** Proportion of caregivers reporting improvement, no change or worsening of caregiver burden at 6 months (observed cases)

### Caregiver burden

At baseline, most caregivers (92.1%) indicated that they considered caregiving a burden: 37.6% rated the burden as mild, 44.1% rated it as moderate and 10.4% rated it as severe. At visit 2, 3 months into rivastigmine therapy, more than three times as many caregivers considered the burden to have lessened than those who considered it to be increased (34.7% vs. 10.6%). At the study's conclusion at 6 months, approximately four times as many caregivers reported a reduced burden than an increased burden (40.3% vs. 10.3%) (Figure 7).

### Use of psychotropic medication

At baseline, there were 491 patients who reported taking antidepressants (23.2% of the total cohort), 400 antipsychotics (18.9%), 302 anxiolytics (14.3%), 143 hypnotics (6.8%) and 34 mood stabilisers (1.6%). At 6 months, of the 1166 evaluable patients, 236 had been taking an antidepressant at baseline



**Figure 8** Changes in regimens at 6 months among patients receiving psychotropic medications at baseline (observed cases)

(20.2%), 217 an antipsychotic (18.6%), 140 an anxiolytic (12.0%), 58 a hypnotic (5.0%) and 16 (1.4%) a mood stabiliser.

Of these patients, most did not have a change in their regimen. More patients either had their dose lowered or discontinued – than had their doses increased (Figure 8). For those patients taking anxiolytics at baseline, for example, 107 of the 140 patients (76.4%) did not have a change in their regimens, while 33 (23.6%) had either a reduction in dose or a discontinuation. It should be noted that there were also a number of patients who were not taking psychotropic medication at baseline who subsequently received such treatment during the study. The numbers of patients with new prescriptions for each of the studied classes were antidepressants, 29; antipsychotics, 36; anxiolytics, 12; hypnotics, 10 and mood stabilisers, 2.

## Discussion

The primary results of this study show that most AD patients, regardless of whether they are treated in the community or in an institution, can benefit from ChEI therapy with rivastigmine.

These ‘real-life’ results add to the clinical trial evidence base with this agent in AD, which includes several earlier-phase, placebo-controlled, randomised trials showing a beneficial effect of rivastigmine treatment (16–18,26).

The emergence and worsening of multiple mood and behavioural symptoms contributes significantly to the high cost, both direct and indirect, associated with the treatment of AD (an estimated \$5.5 billion annually in 2000) (27). Effective treatment with ChEIs may help to reduce this burden.

The symptoms investigated in this study – attention, anxiety, apathy and agitation – were chosen

because of their high prevalence rates and need for treatment. Problems in these areas often arise early in the course of disease and can persist and worsen over time. While historical data have shown that there is significant overlap in these symptoms [a 1996 study reported concurrent symptom presentation in as many as 20% of patients (10)], the present study found that the prevalence of concurrent symptoms was much higher. The proportion of patients with at least two symptoms was 93.5%, including 54.0% who presented with all four. One explanation for this difference is the definition of the presence of symptoms. There can be considerable inter-rater variability in the assessment of symptoms in the absence of a set list of criteria. In the current study, the physicians were provided with definitions for the presence or absence of the four symptoms and it was found that rivastigmine therapy was associated with improvements in agitation and attention in the majority of patients. The number of patients deriving benefit from therapy far outweighed those that did not. Only 6.8% (agitation and anxiety) to 7.7% (attention) of patients had worsening of these symptoms during the trial.

While agitation, anxiety and apathy are all troubling symptoms, difficulties with attention may be particularly problematic in AD, as this can impact many different aspects of daily living. While memory deficits often receive the most scrutiny, non-memory attention-related functions (e.g. ability to concentrate) are also important for carrying out daily tasks. In the current study, more than 90% of patients had attention difficulties at baseline. After 6 months of rivastigmine therapy, most patients either improved (67.5%) or remained the same (24.8%) in this symptom.

Prior evidence shows that rivastigmine may be particularly robust in ADL. In the 2-year EXCEED study, published in 2005 (19), rivastigmine demonstrated statistically significant superiority in efficacy over donepezil on the AD Cooperative Study Activities of Daily Living (ADCS-ADL) scale. Studies in dementia with Lewy Bodies and in Parkinson’s Disease dementia, where deficits in focused and sustained attention are larger than in AD, have also shown that rivastigmine is associated with significant improvements in measures of attention (28,29).

Rivastigmine is a dual inhibitor of both AChE and BuChE (30), both of which are responsible for the hydrolysis of ACh. While AChE is the predominant enzyme in healthy brains, in patients with AD, the activity of AChE declines over the course of disease, while the activity of BuChE increases (2–4). Research has also shown that BuChE is particularly concentra-

ted in subcortical structures (e.g. the limbic system), which are key areas for the regulation of neuropsychiatric symptoms (31).

The fact that many more patients improved than deteriorated on rivastigmine among the institutionalised patients (who typically have more advanced disease) may be interpreted as support for the hypothesis that BuChE inhibition becomes more important as the disease progresses.

In the present study, the most notable change in psychotropic medication was for anxiolytics; 33 of 140 (23.6%) patients taking anxiolytics at baseline either had their doses reduced or discontinued during the trial. No patients required a dose increase. This finding, coupled with the favourable effects of rivastigmine on the symptom of anxiety (62.3% of patients improved vs. 6.8% worsened), suggests that rivastigmine has a considerable anxiolytic effect of its own.

### Study limitations

This study is especially valuable in that it reflects the Canadian experience of how physicians are managing their patients in everyday practice. The open-label design, however, may be associated with physician and/or caregiver bias because of an inherent desire for the patient to improve – a fault common to all open-label studies. This bias may apply to any of the study's outcomes – the abbreviated CGI-C, the MMSE, the caregiver burden and psychotropic drug use – as investigators were aware that each of these was a study outcome.

Moreover, the high drop-out rates, as a result of follow-up compliance, may add bias. High drop-out rates are a common occurrence in open-label studies. In a 2003 open-label evaluation of ChE inhibitor treatment in AD, for example, 73 of 173 patients (42.2%) were evaluable at 1 year (32).

However, evaluation of baseline characteristics of drop-outs showed that they were comparable to the group continuing on in the study. Hence a positive study outcome is not likely due to a higher dropout rate among more severe patients.

In addition, it should be noted that rates of decline in symptoms are heterogeneous among AD patients; comparing outcome data with baseline data may, therefore, be misleading.

Inherent in this type of study is the tendency to have a large percentage of incomplete or missing patient records for the follow-up visits. However, when the reader is aware of the design limitations of a real-life study, he or she is able to interpret the findings accordingly. The limitations inherent in community-based studies do not marginalise the

importance of the information collected from the observed cases.

### Conclusions

The results of the EXACT study reinforce the observation that attention, anxiety, apathy and agitation are all very common symptoms even in mild-to-moderate AD. The majority of patients treated with rivastigmine experienced improvements in each of these four symptoms; this was true for both community-dwelling and institutionalised patients. These real life findings further demonstrate the proven efficacy of rivastigmine in patients with mild-to-moderate AD.

The improvements in anxiety, apathy, agitation and attention were also accompanied by improvements in caregiver burden, a highly desirable outcome in AD management.

The effectiveness of rivastigmine in achieving these results may be partly attributable to its mechanism of action, which is unique among ChEIs. Inhibition of BuChE may help explain rivastigmine's benefit, particularly in those patients with more advanced disease.

The link between improvements in attention seen in this study and improvements in ADL documented elsewhere with rivastigmine is hypothetical and provocative. Testing this hypothesis in a randomised, controlled fashion would be a welcome addition to the evidence base in AD management.

These findings, from a naturalistic, community-based study using simple clinical evaluation tools (i.e. the modified CGI-C) need not be interpreted in isolation as being conclusive proof of rivastigmine's efficacy. Previous placebo-controlled clinical trials have amply demonstrated the efficacy of this agent. However, these results support the use of such simple clinical evaluation tools as a means to identify and monitor common AD symptoms.

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